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A potential multiple resonance mechanism by which weak magnetic fields affect molecules and medical problems: The example of melatonin and experimental ''multiple sclerosis''

Michael A. Persinger *

Behavioral Neuroscience Laboratory, Biophysics Section, Department of Biology, Laurentian University, 935 Ramsey Lake Road, Sudbury, Ont., Canada P3E 2C6

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Summary A biophysical hypothesis to explain the powerful ameliorating effects of weak (nanoTesla range) magnetic fields on melatonin-related diseases is presented. The effects are dependent upon the *molarity* of the melatonin within specific organ spaces. The optimal ameliorating effects upon experimental allergic encephalomyelitis for both the derived intensities (about 35 and 70 nT) and the frequency (7 Hz) were congruent with the empirical observations from previously published and unpublished experiments with rats involving about 1–5000 nT strengths of either 0.5, 7, 40, or 60 Hz magnetic fields. The hypothesis predicts that weaker magnetic fields within the nanoTesla to picoTesla range would optimally affect concentrations of melatonin (in this situation) within the micromolar range and that neurological states (epilepsy) or conditions (ethanol, antidepressants, sleep deprivation) that affect nocturnal melatonin levels in human beings would determine the optimal effective intensity within the 7 Hz range. The resonance solution also suggests that mitochondrial proton gradients may be critical to the process. The model offers an alternative explanation to the variations of Faraday's Law and the Boltzmann constant that have been employed to explain and to dismiss biological effects from weak magnetic fields.
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The problem of current induction and the Boltzmann boundary as the limiting threshold for weak magnetic field effects

The major particles that constitute the functional organization of living systems are associated with electromagnetic fields. Organisms might be considered aggregates of electromagnetic fields that are embedded within or correlated with atomic and molecular structures. They are contained within larger boundaries that define the cell and organ. Variations of Faraday's Law, (a changing magnetic field is associated with an induced changing electric field) and different generations of resonance equations [1–4] have been employed to support and to refute biomagnetic effects. The former

* Tel.: +1 705 674 4824; fax: +1 705 671 3844.
E-mail address: mpersinger@laurentian.ca.

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have been often employed to accommodate the apparently forbidding restraints of the Boltzmann constant which states that at living temperatures a minimum of energy in the order of 10^{-21} J is required to compensate for the apparently structurally obscuring effects from random thermal agitation. However this limit assumes a homogeneous distribution of energy in space and ignores the potentially amplifying or ''focusing'' effects from temporal gradients of energy produced by resonance.

Given the complexity of the many configurations that would result from these correlations between aggregates of electromagnetic fields and their substrates within molecular structures one would expect multiple but *specific* mechanisms by which *applied* electromagnetic fields affect living systems. These mechanisms or processes may or may not compliment the traditional assumptions that any biophysical effect is *simply* a function of the net intensity of the changing magnetic field and the associated induction of an electric field. Intensity may not be the limiting variable. For example, the atmosphere exerts a pressure of 100 kPa. However the human ear, within the range of specific frequencies, can discern massive bits of information presented at pressures (20 mPa) more than a billion times less intense. These small energies are effective because of the application of several ''resonance'' patterns which, when presented *simultaneously*, increase the complexity and contain the information.

Non-linear positive effects on the rat analogue of multiple sclerosis

For the last 10 years we have been investigating the effects of nocturnal application of weak (1–5000 nT, peak-to-peak) amplitude-modulated magnetic fields with discrete frequencies of either 0.5, 7, 40 or 60 Hz, upon the development of experimental encephalomyelitis (EAE), an animal model of multiple sclerosis. A few of these studies were published [5–7]. We have reliably demonstrated that nocturnal exposure for 6 min/h for 8 h every night between midnight and 08 h (late scotophase) to 7 Hz, amplitude-modulated approximately 50 nT fields (see [6] for diagram) produced a powerful reduction in the overt symptoms of the disease as well as the numbers of infiltrations of mononuclear cells within the brain. For some experiments the maximum strength along the inside edges of the coils were about 70 nT. In our specific setting, the applications of the 7 Hz square wave fields through the Helmholtz coils resulted in a 6 min amplitude-varying decrease of the ''static'' or background geomagnetic field within the north–south direction. Superimposed upon this shift were amplitude modulations of the 7 Hz square waves within the 36 and 71 mHz range. They were produced by the intensity increasing in sequential steps seven times during the first 3 min and 20 s and seven times during the last 1 min and 42 s of each 6 min duration. I reasoned that embedding energy from magnetic fields within several expanding and collapsing temporal domains (time intervals) might produce enhanced biological efficacy of very weak magnetic fields in a manner similar to that displayed by large proteins or nucleotides from multiple foldings of molecules within several spatial domains.

In the published studies [5–7] exposures to this frequency at 500 nT intensities or exposures to either 40 or 60 Hz square-wave magnetic fields at either 50 or 500 nT intensities did not ameliorate the symptoms relative to sham-field (less than 10 nT) controls [5,6]. Exposures to the 7 Hz, 50 nT fields during the light phase also did not affect the progression of the disease relative to sham field controls. This diurnal specificity as well as the narrow band of intensity and frequency for the efficacy of the reduction of the intensity of EAE suggested a very specific mechanism that must accommodate the intensity of the applied field as well as its frequency.

Extension of the Jacobson equation for relativistic resonance

Jacobson [8,9] developed a model that might explain this specificity for intensity and frequency. Unlike many resonance theorists he presumed a quantal and relativistic solution should emphasize units of energy rather than Newtonian concepts of force. To predict the strength of the magnetic field that could affect a particular mass, he set the mass of the target molecule (m) multiplied by the speed of light squared (c^2) equal to the product of the strength of the magnetic field (B), the length (l) of the structure to which it is applied, the orbital velocity (v) of the earth, and, charge (q). From this he calculated a series of optimal magnetic field intensities for small and intermediate-sized molecules that ranged within the picoTesla to nanoTesla range using the equation

$$B = mc^2/vlq. \quad (1)$$

From my perspective the generalizability of his model can be increased if the amount of the target mass, in moles, is considered for the calculation of

total charge. This can be accomplished by multiplying the denominator in Eq. (1) by the numbers of molecules contained within different concentrations of the target molecule, such as 1 μM which contains 6.023×10^{17} particles. Realistic solutions for *B* are obtained that may help explain empirical data.

Melatonin as the model molecule

Table 1 contains the exponents for the powers of 10 for strengths of *B* for various concentrations of the molecule *melatonin* [10–13], with a mass of 240 Da, as a function of different amounts and different lengths of the space containing these amounts. Melatonin was selected because this derivative of serotonin, after a single acetylation and methylation, has been shown to be sensitive to very weak (nanoTesla to microTesla) experimental magnetic fields and to ambient changes in geomagnetic activity [2,14].

These values were obtained from the equation. For example, the values would be

$$240\ \text{Da} \times (1.67 \times 10^{-27}\ \text{kg}) \times (9 \times 10^{16}\ \text{m}^2/\text{s}^2),$$

divided by: 30×10^3 m/s $(1.6 \times 10^{-19}$ A s) $\times$ $(6.023 \times 10^{23}$ units/M) $\times M \times l$. The variables would include the concentration, *M*, of melatonin (or the target molecule) and the length, *l*, of organismic space within which the field was operating and the molecule was contained.

For concentrations of melatonin within the microMole to nanoMole range, which are found within many cell systems [10–13], the optimal magnetic field intensity would be within the 10–100 nT range. In our experimental studies we have employed amplitude modulated shifts between about 1 and 70 nT within periods of 6 min once every hour for 8 h (midnight to 08 h) each night. This peak intensity had been selected empirically rather than theoretically because it is within the range of thresholds for disruption of migration in avian species [15] and the experimental induction of epileptic seizures in rats [16].

If we assume 70 nT represents the strength of the field, then the resonance frequency for this mechanism could be calculated. By setting $1/2mv^2/r = Bvq$, where *q* is electric charge, *m* = mass of the particle, and, *r* is the distance, the *r* and *v* terms cancel such that the frequency can be solved with:

$$f = [(Bq)/m]. \quad (2)$$

For the value $[5 \times 10^{-8}\ \text{T} \times 2 \times 1.6 \times 10^{-19}\ \text{C}]$ to obtain solutions in the order of 10 Hz, where the empirical data are most compelling, the unit of mass required would be 1.6×10^{-27} kg, the mass of the proton. To obtain the specific frequency of 7 Hz employed in our studies the predicted strength of the field would be about 70 nT which was within the upper range of our experimentally generated fields. Even if one assumes the critical component is the change in direction of the field generated by the square wave (a ''pulse'') then the strength required for 7 Hz would be 35 nT (half of the value).

Table 1 Effective magnetic field strengths (Tesla) in orders of magnitude according to the equation for various concentrations of melatonin within different lengths (*L*) of biological space

	Field strength (10^*) in Teslas		
Molarity	*L* = 10 cm	*L* = 1 cm	*L* = 1 mm
10^{-3}	−13	−12	−11
10^{-4}	−12	−11	−10
10^{-5}	−11	−10	−9
10^{-6}	−10	−9	−8
10^{-7}	−9	−8	−7
10^{-8}	−8	−7	−6
10^{-9}	−7	−6	−5
10^{-10}	−6	−5	−4
10^{-11}	−5	−4	−3
10^{-12}	−4	−3	−2
10^{-13}	−3	−2	−1
10^{-14}	−2	−1	0
10^{-15}	−1	0	1

Implications for medicine

If these calculations and this hypothesis are valid explanations for the experimental results, there are several implications that are relevant for pursuing the biophysics of complex magnetic field effects upon biological systems. First, as noted in Table 1, the more concentrated the target molecule the *less* intense the temporally appropriate shift in the steady state magnetic field required to produce the optimal effect. At concentrations within the millimole to micromole range, which characterize many biologically relevant chemical and molecular species, field intensities within the picoTesla range would be sufficient [8]. Sandyk [17–19] and his colleagues [2] have repeatedly emphasized the importance of these weak magnetic fields and have suggested that the brain itself operates within the this range.

Similarly the solutions predict that very intense shifts (1 T) in the steady background magnetic field, within the range employed for magnetic

resonance imagining (MRI), would optimally affect melatonin in spaces where the concentration is within the femtomole range. From the perspective of the current measurements for melatonin, for example, this would imply that the 1 T fields would affect many organs diffusely because of the extremely low (trace) concentrations of this compound throughout the body. However the nanoTesla and picoTesla magnetic field shifts would primarily affect only those short spaces, such as the pineal organ [12], and some longer spaces, such as the gastrointestinal system [10], where the concentrations are highest.

The second implication generated from the equation is that, for a given molarity, as the length increases the intensity of the shift in the steady state field required to affect that concentration becomes less. Length in this model is assumed to refer to the distance between boundary conditions (the width of the organ) containing the concentration of the molecule. For the rat pineal organ (about 1 mm), the approximate concentration of melatonin would be within the micromole range.

The third implication is that any condition that increases the concentration of melatonin within the boundary would *lower* the required intensity of the field with the optimal frequency to produce the effect. Nocturnal levels of melatonin are about 100 times the level of daily values. This differential would be consistent with our observations that only the 10—70 nT (median 30—50 nT), 7 Hz magnetic fields only diminished the symptoms of EAE when presented during the night but not during the day. The latter, according to the equation, would have required field strengths 100 times larger (5 μT or 50 mG) to be effective.

Consequently, biogenic or exogenously-induced variations in concentrations of melatonin could *determine* the optimal magnetic field strengths and frequencies required to produce maximum effects. For example increased melatonin production has been measured in untreated epileptic patients. Increased levels of nocturnal melatonin follow consumption of moderately low dosages of ethanol and sleep deprivation [20]. Some antidepressants such as desimipramine and oral contraceptives such as progestin increase nocturnal melatonin levels while common antipsychotic drugs such as clonidine, benzodiazepines such as alprazolam, and adrenergic β blockers such as atenolol, decrease melatonin levels [21].

The fourth implication is that the protons within melatonin or from sources with which it interacts are responsible for the resonance effect. If these protons are from the populations driven across the membrane (to produce the H+ gradient) from the inner mitochondrial compartments [22] and are derived from energy from the successively lower energy states of electrons within NADH (formed from nicotine adenine dinucleotide and a hydride ion) and FADH2 (reduced flavin adenine dinucleotide), then the role of these organelles in the mediation of weak (nanoTesla, microTesla) magnetic field effects may be more important than previously assumed. Affecting the proton gradient would also influence a plethora of energy-requiring reactions that could explain the consternation of the multiplicity and ''diffuseness'' of many weak magnetic effects.

Considerations for calcium

However there would another potential resonance effect generated by the experimental field. Changes in field strengths within 15—20 nT range at functional frequencies between 0.036 Hz (36 mHz) and 0.071 Hz (71 mHz), the amplitude modulation component of our experimentally-generated 6 min-field, would be congruent with the mass of the calcium ion (and adjacent elements in the Periodic Table). Extremely low frequency calcium resonance has been shown to depress melatonin synthesis in the pineal organ [2]. It is possible that the optimal mechanism by which weak magnetic fields affect chemical structures may require the simultaneous application of more than one resonance targeted at the chemical process.

What appears to be an unusual inclusion (the orbital velocity of the earth) in Jacobson's relations is less anomalous when the similarities between the duration of two resonant oscillations between the solid earth and the atmosphere and their potential relationship to the resultant orbital velocity of the earth are considered [23]. These solutions are within mHz ranges that also dominate the power spectral density of geomagnetic activity [4]. Interestingly, they were also generated within and between the 6 min presentations of our experimental fields [5—7].

If the results predicted by variations of Jacobson's equation are generalizable, then the accurate prediction of the biochemical effects relevant to medical phenomena from exposure to weak but temporally structured magnetic fields may require the inclusion of variables traditionally ignored or excluded from analyses. The specific temporal complexities of magnetic fields would be the analogues of the specific spatial complexities of molecular (chemical) structures. Both forms of complexity, like complimentary sides of a biological coin, could produce the same effects. For optimal

molecular effects the matching of the concentrations with the appropriate K_D (dissociation constant) value for the receptor subtype is essential. For optimal magnetic field effects the present hypothesis suggests a similar requirement for specificity that, like the efficacy of high affinity receptors, is non-linear and occasionally counterintuitive [24].

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References

[1] Engstrom S, Fitzsimmons R. Five hypotheses to examine the nature of magnetic field transduction in biological systems. Bioelectromagnetics 1999;20:423—30.
[2] Lerchl A, Reiter RJ, Howes LA, Nonaka KO, Stokkan K-A. Evidence of extremely low frequency Ca++ resonance depresses pineal melatonin synthesis in vitro. Neurosci Lett 1991;91:213—5.
[3] Liboff AR, Smith SD, McLeod BR. Experimental evidence for ion cyclotron resonance mediation of membrane transport. In: Blank M, Findl E, editors. Mechanistic approaches to interactions of electric and electromagnetic fields with living systems. New York: Plenum; 1987. p. 109—32.
[4] Ludwig HW. A hypothesis concerning the absorption mechanisms of atmospherics in the nervous system. Int J Biometeor 1968;12:93—8.
[5] Cook LL, Persinger MA. Suppression of experimental allergic encephalomyelitis is specific to frequency and intensity of nocturnally applied, intermittent magnetic fields in rats. Neurosci Lett 2000;292:171—4.
[6] Cook LL, Persinger MA. Differential effects of low frequency, low intensity nocturnal magnetic fields upon infiltration of mononuclear cells and numbers of mast cells in Lewis rat brains. Toxicol Lett 2000;118:9—19.
[7] Kinoshameg SA, Persinger MA. Suppression of experimental allergic encephalomyelitis in rats by 50 nT, 7 Hz amplitude-modulated nocturnal magnetic fields depends on when after inoculation the fields are applied. Neurosci Lett 2004;370:166—70.
[8] Jacobson JI. Pineal-hypothalamic tract mediation of pico-Tesla magnetic fields in the treatment of neurological disorders. Pan Nerva Med 1994;36:201—5.
[9] Jacobson JI, Yamanashi WS, Brown B, Parekh P, Shin D, Saxena BB. The Center for Frontier Sciences 2000;9:6—11.
[10] Bubenik GA. Gastrointestinal melatonin: localization, function, and clinical relevance. Dig Dis Sci 2002;47:2336—48.
[11] Bubenik GA, Blask DE, Brown GM, Mestroni JM, Pang SF, Reiter RJ, et al. Prospects of the clinical utilization of melatonin. Bio Signals Recept 1998;7:195—219.
[12] Foley PB, Cairncross KD, Foldes A. Pineal indolamines: significance and measurement. Neurosci Biobehav Rev 1976;10:273—93.
[13] Hardeland R. New actions of melatonin and their relevance to biometeorology. Int J Biometeor 1997;41:45—57.
[14] Burch JB, Reif JS, Yost MG. Geomagnetic disturbances are associated with reduced nocturnal excretion of a melatonin metabolite in humans. Neurosci Lett 1999;266:209—12.
[15] Semms P. The magnetic detection system of the pigeon: involvement of the pineal and retinal photoreceptors and the vestibular system. In: Connor ME, Lovely RH, editors. Electromagnetic fields and neurobehavioral function. New York: Liss; 1998. p. 47—61.
[16] Michon AL, Persinger MA. Experimental simulation of the effects of increased geomagnetic activity upon nocturnal seizures in epileptic rats. Neurosci Lett 1997;224:53—6.
[17] Sandyk R. Successful treatment of multiple sclerosis with magnetic fields. Int J Neurosci 1992;66:237—50.
[18] Sandyk R. Therapeutic effects of alternating current pulsed electromagnetic fields in multiple sclerosis. J Altern Complemen Med 1997;3:365—86.
[19] Anninos PA, Tsagas N, Sandyk R, Derpapas K. Magnetic stimulation in the treatment of partial seizures. Int J Neurosci 1991;60:141—71.
[20] Badia P, Murphy PJ, Myers BL, Wright KP. Alcohol ingestion and nighttime melatonin levels. Sleep Res 1994;23:477.
[21] Myers B, Badia P. Factors affecting endogenous melatonin levels. Sleep Res 1993;22:2.
[22] Alberts B, Johnson D, Lewis J, Raff M, Roberts K, Walter P. The cell. New York: Garland; 2002.
[23] Booth JN, Koren SA, Persinger MA. Increased feelings of the sensed presence and increased geomagnetic activity at the time of the experience during exposures to transcerebral weak complex magnetic fields. Int J Neurosci 2005;115:1039—1065.
[24] Persinger MA, McKay BE, O'Donovan CA, Koren SA. Sudden death in epileptic rats exposed to nocturnal magnetic fields that simulate the shape and the intensity of sudden changes in geomagnetic activity: an experiment in response to Schnabel, Beblo and May. Int J Biometeor 2005;49:256—61.

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